

## REMARKS

Applicants have amended claim 1 to make explicit that which was implicit, namely that the method is directed to quantification of the amount of the nucleic acid (for support, see, e.g., par. [003] and [0026]) and use of single base extension reaction (for support, see, e.g., Figure 1). Claims 4-9 are cancelled. Accordingly, no new matter has been introduced by the amendments and their entry is respectfully requested.

Applicants now turn to the specific rejections.

The Examiner rejected claims 1-3 and 10-13 as allegedly unpatentable under 35 U.S.C. 103(a) over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102) and Ross et al. (BioTechniques, September 2000, vol. 29, pages 620-629).

Applicants respectfully disagree and submit that the rejection should be withdrawn for the following reasons.

Applicants respectfully submit that the rejection should be withdrawn for the following reasons.

Applicants have amended the claims to make explicit that which was implicit, namely that the present method is directed to quantification of the amount, not relative quantification, and that the quantification is performed using a single base extension reaction. A **quantification** method that results in **an amount of the nucleic acid** in the sample is different from the **relative quantification method of Ross**, which only results in determining how big a percentage of the total nucleic acids in the sample contains the specific allelic variant in question.

The Examiner contends that "[o]ne of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNUPE (single nucleotide primer extension), have been well-established."

However, in stating this, the Examiner ignores Ross as a whole and the Declaration by Dr. Ding submitted with the amendment dated September 10, 2007. Dr. Ding specifically addressed the problems known to skilled artisans when using MALDI TOFF MS and why a skilled artisan would not have expected the claimed method to work. Dr. Ding also testified that the inventors themselves found it surprising that the method was capable of differentiating the

**small size differences** as well as allowing to quantify the amount of nucleic acids using single base extension reaction.

At page 622, first column, under “Results”, also Ross specifically teaches that they used a **“modified single-base primer extension reaction”** to overcome the **expected problem** in accurate determination of alleles in presence of excess of another allele (emphasis added). Ross specifically states that “baseline resolution between alleles differing by 16 Da or less **may not be observed**” (page 622, emphasis added). Ross also mentions that “area measurement of a low-intensity extension product within 40 Da of another allele **may be confounded by trace cation**” (page 622, emphasis added). Thus, contrary to the Examiner’s conclusion based on partial reading of Ross, **Ross did not expect a single-base pair extension reaction to work** precisely at resolving small differences and would not expect it to work when using MALDI-TOFF. Thus, Dr. Ding’s statement about the expected resolution problems and his surprise in observing that this method actually worked with a regular primer extension method is further confirmed by Ross. While Ross did mention that their results “form a basis for future investigation” for multiplex experiments, this does not in any way indicate that such multiplex reactions would be successful using a **single base** primer extension reaction. Rather, the conclusion refers to their method, in which a **modified base extension reaction** was used to avoid the anticipated problems in using MALDI TOFF in connection with single base extension reaction.

Therefore, Applicants respectfully submit that, if anything, Ross teaches away of the presently claimed method of using a single base extension reaction.

In view of the amendments to the claims and the arguments above, Applicants respectfully submit that the rejection of claims 1-3 and 10-13 under 35 U.S.C. 103(a) over Becker in view of Amexis and Ross should be withdrawn.

The Examiner also provisionally rejected claims 1-3 and 10-13 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-12 of co-pending Application No. 10/589,709. Applicants will submit a Terminal Disclaimer regarding Application Serial No. 10/589,709 should the claims be otherwise in condition for allowance.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance.

Early and favorable action is respectfully requested. Applicants encourage the Examiner to contact the undersigned attorney should he have amendment suggestions that may expedite allowance of the claims.

In the event that any additional fees are required, the Commissioner is hereby authorized to charge Nixon Peabody LLP deposit account No. 50-0850.

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Respectfully submitted,

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